REMARKS

Withdrawal of the rejection of claims 1, 10, 16, 17 and 20 under 35 U.S.C. 102 (b) is acknowledged.

Rejection of claims 1-22 under 35 U.S.C. 103 (a)

Examiner maintained his rejection of all pending claims under 35 U.S.C. 103 (a) as being unpatentable over Li et al. in view of Jimenez et al. Examiner dismissed Applicant's arguments with the following comments: "As the applicant himself has stated in the arguments filed 12 May 2003, the rejection set forth in the previous office action may read on one member of the Markush group in claims 2, 4, 7, 9, 13, 15, and 22. Rejection of one member of a Markush group, in accordance with Office policy, is sufficient for an obviousness-type rejection under 35 U.S.C. 103, since each member of the Markush group is recognized as belonging to a broader class recognized by the art. Thus, the rejection under 35 U.S.C. 103 previously set forth is deemed proper and will be maintained". Examiner misinterpreted Applicant's comments. Applicant did not make any such admission. He simply responded to Examiner's rejection of all claims that was apparently based on Examiner's belief that "an activated HSF1 in nucleic acid or protein form" is patentably indistinguishable from "a nucleic acid comprising an expression vector capable of expressing human p-glycoprotein" by pointing out that "activated HSF1" was exclusively appearing in the Markush-type claims 2, 4, 7, 9, 13, 15, and 22. See Applicant's response on p.5, lines 1-4. Nowhere in the response did Applicant concede that "activated HSF1" and human p-glycoprotein were patentably indistinguishable. On the contrary, Applicant provided clear arguments that distinguished the two proteins (and nucleic acids encoding them). See Applicant's response on p.5, line 5 to p.6, line 3. Applicant would like to reiterate that activated forms of HSF1 and human p-glycoprotein are patently distinct "therapeutic agents", because they are structurally (e.g., by amino acid sequence) and functionally unrelated. Consequently, uses of the two types of agents are also patentably distinct. Activated forms of HSF1 are mutant forms of nuclear-localized transcription factor HSF1. In contrast to the wildtype factor, the mutant forms are transactivation-competent when expressed. Activated HSF1 transactivates a group of endogenous genes encoding stress proteins Hsp110, Hsp90, Hsp70, Hsp60,

Hsp25-27 and Hsp10. Most of these proteins are well known to individually (or Hsp60 and Hsp10 in combination) have a cytoprotective effect in certain mammalian cell types. In certain cell types, activated HSF1 also transactivates additional genes such as genes encoding c-Fos, steroid-responsive genes, FKBP52, p-glycoprotein or hemoxygenase; inhibition of gene expression by HSF1 is also known. Embodiments of Applicant's method comprise the topical use of activated HSF1 to trigger the above-mentioned multitude of changes in gene expression, which changes have the desired effect of protecting hair follicles against the toxicity of chemotherapeutic agents. Human p-glycoprotein is a membrane-bound human protein that acts as a pump of hydrophobic compounds, including certain chemotherapeutic agents. It is noteworthy that, to Applicant's knowledge, no information was available at the priority date of the instant application on whether over-expression of p-glycoprotein would be capable of preventing or reducing chemotherapy-induced hair loss.

Examiner had rejected claims 1-22 under 35 U.S.C. 103 (a) as being unpatentable over Li et al. in view of Jimenez et al. For an obviousness-type rejection based on a combination of two references, the rejection is only proper, if at least one of the references suggests the combination. Li et al. is concerned with an improved method for delivery of agents to hair follicles using low-frequency vibration. Except for an example relating to ablation of hair, the patent is limited to a description of the improved delivery method and a listing of agents that might be delivered using the method. This also includes a laundry list of proteins/genes (column 4, lines 50-56) to be delivered by the improved delivery method that inventors speculated to be helpful in inhibiting chemotherapy-induced alopecia. Nothing beyond this listing is provided. Hence, the Li et al. patent stands for an improved method of delivery to hair follicle cells. Because no indication was provided that the method would, in fact, even be capable of delivering nucleic acids, the patent could be considered as furnishing an invitation for experimentation that would determine whether nucleic acids could be delivered to hair follicles. It could, possibly, even be cited for inviting experimentation to test whether expression vectors for various particular proteins including p-glycoprotein could be delivered. To cite the patent for inviting experimentation relating to "methods useful for the prevention of hair loss during

chemotherapy" or even for "teaching" such methods represents unreasonable boot-strapping based entirely on hindsight. Except for a sentence expressing the wishful thinking of the inventors (column 4, lines 56-62), the patent does not relate to methods of treatment of chemotherapy-induced alopecia. Ostensibly, the inventors were not even sufficiently enamored by their speculation to claim p-glycoprotein or a p-glycoprotein expression vector as agents to be delivered by the improved method of delivery. This is particularly striking as claims (see claims 9 and 11) recite the entire laundry list of potential anti-alopecic agents of column 4 with the singular exception of p-glycoprotein. Because the Li et al. patent does not reasonably relate to a method of prevention of chemotherapy-induced alopecia, it is also incapable of providing any motivation for making the combination with the Jimenez et al. reference. The Jimenez et al patent relates to methods of inhibiting chemotherapy-induced alopecia by vitamin D3 or metabolites of vitamin D3. The patent is specific to these compounds and certain growth factors. Nowhere in the patent is the use of p-glycoprotein or a p-glycoprotein expression vector mentioned. Hence, the Jimenez et al. reference does not suggest a combination with the Li et al. reference. Therefore, because there is no reasonable basis for combining the two cited references, Examiner is respectfully requested to withdraw his rejection of all claims under U.S.C. 103 (a).

Rejection of claims 1-15, 21 and 22 under 35 U.S.C. 112, first paragraph

Examiner offered two rationales for rejecting the above-listed claims. First, he concluded that the claims are rejected "under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diamide, geldanamycin, sodium arsenite, stannous chloride, zinc chloride, and an activated heat shock transcription factor 1 in protein or nucleic acid form, does not reasonably provide enablement for all benzoquinone ansamycin compounds, all arsenic salts, all tin salts, and all zinc salts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims". Second, Examiner attempted to determine "whether (the) disclosure meets the enablement requirement" by carrying out an analysis of the factors described in *In re*

Wands and concluded "that one skilled in the art could not practice the invention without undue experimentation".

With respect to the first rationale offered, Applicant observes that his claims can be separated into two distinct groups. Independent claims 1, 10 and 21 accurately describe what Applicant regards as an important embodiment of his invention. In essence, his invention as described in these claims relates to a method (or composition in claim 21) for protection against chemotherapy-induced alopecia involving the topical application to the scalp of a patient or skin of an animal of an effective amount of a chemical inducer of the stress protein response sufficiently prior to the administration of a chemotherapeutic drug. The method is supported by a detailed description of the method in the specification, by working examples and by a sufficient disclosure of a representative number of compounds that can function as "chemical inducer of the stress protein response". As Examiner himself had conceded in his Office Action, the specification is "enabling for diamide, geldanamycin, sodium arsenite, stannous chloride, zinc chloride, and an activated heat shock transcription factor 1 in protein or nucleic acid form". See the above-cited paragraph of the Office Action. Hence, based on these facts, Applicant should be entitled to these independent claims as well as to any dependent claim that does not name specific inducers (claims 3, 5, 6, 8, 11, 12, 14, and 21). Applicant respectfully requests that Examiner withdraw his rejection of the above independent claims as well as of the latter group of dependent claims.

The second group of claims includes all claims, in which named inducers are listed, i.e., claims 2, 4, 7, 9, 13, 15 and 22. Examiner stated that, e.g., geldanamycin but not all benzoquinone ansamycins are enabled. Similar objections were made for all arsenic salts, all tin salts and all zinc salts. Claims 2, 4, 7, 9, 13, 15 and 22 all contain the phrase "a chemical inducer of the stress protein response selected from the group consisting of diamide, a benzoquinone ansamycin, an arsenic salt, a tin salt, a zinc salt and an activated HSF1 in nucleic acid or protein form". Hence, not all benzoquinone ansamycins, arsenic salts, tin salts and zinc salts are claimed, but only those that can act as chemical inducers of the stress protein response. Examiner is referred to the specification between p.15, line

8 and p.16, line 4, where it is explained what an inducer is, and how it can be readily determined whether a compound is an inducer. Therefore, Applicant believes that his Markush-type claims are properly enabled over their entire scope. Applicant respectfully requests that Examiner also withdraw his enablement rejection of this second group of claims.

Regarding Examiner's analysis of factors according to *In re Wands*, Applicant appreciates that Examiner attempted to decide the question of undue experimentation by taking into consideration more than one factor. However, Applicant respectfully disagrees with important aspects of Examiner's analysis and, consequently, traverses the conclusion reached by the Examiner.

Regarding "the nature of the invention", for the purpose of the present response, Applicant agrees with Examiner's characterization as it pertains to the claims rejected under 35 U.S.C. 112.

Concerning "the state of the prior art", Applicant respectfully traverses Examiner's characterization of the state of the prior art. Except for his comment relating to a relatively low volume of research dealing with mechanisms by which chemotherapeutic agents cause alopecia, Examiner appears to have defined the relevant prior art narrowly as methods of treatment of chemotherapy-induced alopecia. He then recited the various shortcomings of known methods, which shortcomings are specific to these methods as one skilled in the art will readily recognize. As explained in the Training Material of the Patent Office, "the pertinent art should be defined in terms of (not as) the problem to be solved". Hence, the prior art, more properly viewed, should be the field of alopecia research and, because the invention makes the combination, the field relating to research on the stress protein response. Although the search for effective therapeutic methods is still ongoing, the field of alopecia research is a long-established field that developed many validated research methods and tools. For example, as alluded to under "Background" and in the section "Animal Models of Chemotherapy-induced Alopecia", several animal models for testing methods of chemotherapy-induced alopecia were

developed and validated in various studies over a period of about ten years. Furthermore, several human trials were conducted that tested different protocols for their effectiveness in preventing/reducing chemotherapy-induced alopecia. How human hair grows and the differences between hair growth in humans and other mammals have been well researched. Regarding mechanisms of chemotherapy-induced alopecia, it is likely that cytotoxic agents kill hair follicle cells by the same (known) mechanisms, by which they kill tumor cells and other proliferating cells. Hence, the prior art is highly developed as far as the understanding of hair growth, recognition/quantitation of alopecia and chemotherapy-induced alopecia, and detailed, validated methodology for testing the efficacy of a compound for reducing alopecia in animal models or in humans are concerned. The stress protein research field is a similarly well-established field. Many compounds and physical conditions that induce the stress protein response are known from numerous cell culture and in vivo studies. The same studies also defined effective concentrations of compounds that act as inducers of the stress protein response as well as provided various methods for identifying inducers.

Regarding "the relative skill of those in the art", for the purpose of the present response, Applicant agrees with Examiner's characterization that the relative skill level is high.

Regarding "predictability and unpredictability of the art", Applicant observes that this inquiry should be extended to the prior art as more properly defined above. When applied to the established fields of alopecia and stress protein response research, the conclusion can only be that there is a high degree of predictability. Examiner argued that "in methods of preventing a condition, the time-dependence factor cannot be easily predicted". Applicant respectfully disagrees with this argument as applied to his invention. It was well known in the art that when a cell is exposed to a moderate physical stress or an appropriate concentration of a chemical inducer, it begins to incease its levels of stress proteins within several hours and thereby acquires a cytoprotected state. If one additionally allows for a certain time period for penetration into hair follicles of a chemical inducer from a composition applied topically to the skin, one can readily estimate an approximate delay between administration of an inducer-containing

composition and exposure to an alopecia-causing chemotherapeutic agent. Applicant has provided ranges of this time factor in the specification, e.g., on p. 4, lines 2-10, p.5 lines 3-6 and line 31 to line 2 of p.6, p.19, lines 12-20, p.20, line 31 to p.21, line 3, and in claims 5, 6, 11, 12, 18 and 19. Applicant also observed in his experimentation that time factors chosen from the middle of the ranges provided in the claims (see, e.g., claims 5, 6, 18 and 19) provide adequate protection against chemotherapy-induced alopecia. Delays of 16-19 hours after administration of a chemical inducer and 9-11 h after administration of physical inducer heat were entirely adequate. Examiner further stated that "as the background section of the Jimenez et al. patent reveals, therapeutic agents must be tested for effectiveness against specific, individual chemotherapy agents". Applicant carefully read and reread the indicated section of the Jimenez et al. patent, but was unable to locate any statement to this effect. In fact, such a statement does not appear anywhere in the patent. Perhaps, the Examiner remembered Applicant's own disclosure on p.27, first paragraph, where Applicant proposed to use chemotherapeutic drugs individually in model experiments, for reasons of experimental clarity only. Please note that the specification does not describe different methods for different chemotherapeutic agents, but consistently teaches that the method of the invention induces a stress protein response in hair follicles, which response is protective against cytotoxic effects of chemotherapy agents. See, for example, the sentence on p.7, lines 19-22: "The present invention relates to deliberate localized induction of the stress protein response in the scalp of a patient or the skin of a mammalian animal in need of chemotherapy to protect hair follicles against the cytotoxic effects of chemotherapeutic agents and combinations thereof without compromising the therapeutic efficacy of the latter agents". In his experimentation with the newborn rat model, Applicant found that a single dose of a physical or chemical inducer is capable of effectively protecting hair follicles against a subsequent administration of any of several chemotherapeutic agents. It is noted that the agents tested included the three agents that are of predominant concern to clinicians, because they cause severe alopecia and are among the most frequently used drugs in chemotherapy regimes.

Regarding "the breath of the claims", Applicant's claims are narrow in the sense that they seek to protect only what Applicant's invention entails. Applicant's invention comprises a topical activation of the stress protein response in the scalp of a patient or the skin of an animal to protect the patient or animal against chemotherapy-induced hair loss in the latter locations. This is what Applicant seeks to protect. Regarding chemical inducers used in the method of the invention, these molecules are clearly defined as molecules that are capable of activating the stress protein response. That a considerable number of chemical inducers that can be used in the practice of the invention are either known in the art or can readily be identified does not render the claims more broad but simply reveals the advanced state of the art. To adequately protect his invention, Applicant should be entitled to claim the practice of his method using any known or readily identifiable chemical inducer that activates the stress protein response. See In re Goffe cited in the "Training Materials for Examining Patent Applications with Respect to 35 U.S.C. 112, First Paragraph-Enablement": "to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress of the useful arts".

Regarding "the amount of direction or guidance presented", the specification including the examples presented therein provide extensive guidance. As was discussed above, functional time ranges are provided for the delay between administration of a physical or chemical inducer and chemotherapy. A selection of chemical and physical inducers is discussed, mechanisms by which they activate the stress protein response are explained, and methods for identifying additional inducers are provided. Penetration enhancers and carriers known to be effective in delivery to hair follicles are disclosed. Established animal models for chemotherapy-induced alopecia are described, and the employment of these models for optimizing parameters of the method of the invention is explained by way of model experiments. Extensive guidance is provided on assessment of hair loss and on alternative criteria for testing the effectiveness of the method both in animals (in the sections "Animal Models of Chemotherapy-Induced Alopecia" and "Model Experiments

for Establishing Conditions for Optimal Protection of Hair Follicles against Selected Chemotherapeutic Agents") and in human clinical studies (p.18, line 31 to p.19, line 7). Detailed explanations are provided for approaches for determining effective doses of inducers (in the sections "Animal Models of Chemotherapy-Induced Alopecia" and "Model Experiments for Establishing Conditions for Optimal Protection of Hair Follicles against Selected Chemotherapeutic Agents"). The specification further discloses that ranges of concentrations of chemical inducers that cause a detectable stress protein response in mammalian cell cultures are known in the art and can serve as initial guides for dose-finding studies (p.18, lines 22-24). A representative publication providing example doses for a range of typical inducers is provided (p.18, line 24) and incorporated by reference (p. 30, lines 18-19).

Regarding "the presence and absence of working examples", Examiner agreed that Applicant disclosed experimental protocols in detail and provided actual results demonstrating the effectiveness of the instantly claimed invention for two chemical inducers.

"The quantity of experimentation necessary". To practice the invention in human patients, a standard clinical dose-finding study will need to be carried out for the chosen inducer-containing composition. As discussed above, functional time ranges are provided in the specification for the delay between administration of a physical or chemical inducer and chemotherapy. The clinical dose-finding study represents routine experimentation because both methodology to be used and appropriate endpoints to be measured are well known from the art and the specification.

In summary, on the one side, there is a highly developed state of the prior art. Consequently, there is a high degree of predictability of the art. The relative skill of those in the art is high. On the other side, claims are defined as narrowly as possible to encompass the invention and to adequately protect the inventor. Extensive guidance is provided by the instant application, especially when supplemented with the known art. Working examples are provided, and only routine dose-finding experimentation is

required. Weighing these factors can only lead to the conclusion that the claims in question are fully enabled and that no undue experimentation is required. Examiner is, therefore, respectfully requested to withdraw his rejection under 35 U.S.C. 112.

Applicant believes that the application is in condition of allowance, and a response to that effect by the Examiner is respectfully requested.

Examiner is cordially invited to call Applicant at (305) 243-5815 if he believes that a further discussion would be helpful for advancing this case.

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Respectfully Submitted,

Richard Voellmy, Applicant & Attorney
Reg. No. 40,859